PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RVCW/P28940PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/03894	International filing date *(day/month/year)* 08.09.2003	Priority date *(day/month/year)* 07.09.2002
International Patent Classification (IPC) or both national classification and IPC A61K35/28		
Applicant THE ROYAL VETERINARY COLLEGE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.04.2004	21.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Pilling, S Telephone No. +49 89 2399-8461

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International application No. PCT/GB 03/03894

I. **Basis of the report**

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-39 as originally filed

Claims, Numbers

1-13 received on 24.09.2004 with letter of 23.09.2004

Drawings, Sheets

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-10,13

because:

☒ the said international application, or the said claims Nos. 1-10,13 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11
	No:	Claims	12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	11,12
Industrial applicability (IA)	Yes:	Claims	11,12
	No:	Claims	

2. Citations and explanations

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see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

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Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1 to 10 and 13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no international preliminary examination will be made in respect of these claims (Article 34(4)(a)(i) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D8 in the order of their listing.

3. The relevant disclosures of the documents cited in the ISR are summarised as follows;

document D1 discloses the injection of liquid suspensions of mesenchymal stem cells (MSCs) for regenerating cartilage tissue in the joint including meniscal tissue (see page 4 line 26 to page 5 line 14, Example 1 and Claims 7 and 26)

document D2 discloses the injection of liquid suspensions of MSCs to repair articular cartilage tissue including spinal disc cartilage (see page 4 line 30 to page 5 line 9, page 6 lines 1 to 9, page 17 lines 11 to 21, Claims 1, 11, 12)

document D3 discloses injection of liquid suspensions of tenocytes (optionally genetically modified) for repairing tendon/ligament defects (see the abstract, page 6 line 31 to page 7 line 16, Example 5, Claims 1, 4 and 23)

document D4 discloses the injection of liquid suspensions of MSCs and reports that the MSC's migrate to artificially induced cartilage and tendon injuries (see whole document)

document D5 discloses that artificially induced ligament defects can be treated by injection of liquid suspensions of MSCs (see abstract and "materials and methods").

document D6 to D8 (see the passages cited in the ISR) shows that the implantation of MSCs (although not in the form of liquid suspensions) in order to treat tendon/ligament defects is conventional.

Claim 11; use of a composition of mesenchymal stem cells..Etc

4. None of the presently available prior art documents discloses the subject matter of present Claim 11. Thus, the subject matter of Claim 11 is new (Article 33(2) PCT).

5. Nevertheless, it is considered that the subject matter of Claim 11 lacks inventive step for the following reasons; Each of documents D3 to D5 teach that liquid suspensions of MSCs/ tenocytes may be used to treat tendon/ligament injuries. Although each of these documents may not disclose treatment of natural injuries, *i.e.* they relate to experimental models, and may also not disclose treatment of horses, it is considered that the extrapolation of the results of documents D3 to D5 to include treatment of natural injuries in horses would inevitably occur to one of skill in this art. In this regard, experimental studies relating to artificially induced injuries are clearly designed to provide treatment for natural injuries. Moreover, the selection of further mammalian species for treatment is not sufficient to provide the necessary inventive step. It is further noted that the teachings of D3 to D5 are further supported by the teachings of each of documents D6 to D8 which provide further teaching toward the use of MSCs to treat tendon/ligament injuries.

6. Thus, the subject matter of Claim 11 is not inventive in view of the disclosures of each of documents D3 to D8 as summarised herein above (Article 33(3) PCT).

7. With reference to D3, it may be helpful to note that the method of obtention of the tenocytes defined in Claim 11 cannot characterise this second medical use claim. This claim is not directed towards a method of obtaining tenocytes but rather to a second or subsequent medical use of tenocytes.

Claim 12; A kit of parts comprising..Etc

8. The definitions in Claim 12 of "*means for delivering the liquid suspension..Etc*" and "*means for determining that the means for delivering..Etc*" are vague and unclear leading to lack of clarity (Article 6 PCT). These vague and unclear terms have not been taken into account when assessing the novelty of Claim 12.

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9. Each of documents D1 to D5 at least disclose liquid suspensions of MSCs and means for delivering them to injury sites. Thus as far as can presently be determined, it appears that the subject matter of Claim 12 lacks novelty in view of the disclosures of each of these documents (Article 33(2) PCT).

CLAIMS

1. A method of treating a natural tendon or ligament injury in a patient the method comprising administering to the patient a composition of mesenchymal stem cells in liquid suspension enriched compared to the natural source of said cells, or tenocytes derived therefrom, wherein the patient is a horse.

2. A method according to Claim 1 wherein the injury is strain induced.

3. A method according to Claim 1 or 2 wherein the composition of mesenchymal stem cells or tenocytes is administered at the site of tissue injury.

4. A method according to any one of Claims 1 to 3 wherein the tendon or ligament is selected from the group consisting of superficial digital flexor tendon (SDFT), suspensory ligament, deep digital flexor tendon, meniscus, cruciate ligament, and accessory ligament of the deep digital flexor tendon.

5. A method according to any one of the preceding claims wherein the mesenchymal stem cells or tenocytes are allogenic.

6. A method according to Claim 5 wherein the mesenchymal stem cells or tenocytes are autologous.

7. A method according to Claim 6 wherein the mesenchymal stem cells are derived from the bone marrow of the patient.

8. A method according to Claim 6 wherein the mesenchymal stem cells are derived from umbilical cord blood previously recovered from the patient.

9. A method according to any one of the preceding claims wherein the liquid suspension of mesenchymal stem cells or tenocytes is injected.

10. A method according to any one of the preceding claims wherein biological signals which encourage the mesenchymal stem cells to form tenocytes are also amdministered to the patient.

11. Use of a composition of mesenchymal stem cells in liquid suspension enriched compared to the natural source of said cells, or tenocytes derived therefrom, in the manufacture of a medicament for treating a natural tendon or ligament injury in a patient, wherein the patient is a horse.

12. A kit of parts comprising (1) a composition of mesenchymal stem cells in liquid suspension enriched compared to the natural source of said cells, or tenocytes derived therefrom, (2) means for delivering the liquid suspension of stem cells to a site of natural tendon or ligament injury in a patient which is a horse and (3) means for determining that the means for delivering locate to the site of injury.

13. A method according to any one of Claims 1 to 10 wherein the site of injury is cleansed of damaged tissue and any early repair scar tissue starting to form at the site before administration of the composition of mesenchymal stem cells or tenocytes.